

NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC™)
GUIDELINE SYNTHESIS

Use of Colony Stimulating Factors in Patients Receiving
Chemotherapy

Guidelines

1. American Society of Clinical Oncology (ASCO). [2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines](#). American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 2000 Oct 15; 18(20):3558-85. [165 references].
2. Practice Guidelines Initiative (PGI). [Role of colony-stimulating factor in patients receiving myelosuppressive chemotherapy for treatment of cancer](#). Curr Oncol 2003; 10(2): 102-26. [76 references]

INTRODUCTION:

A comparison of ASCO and PGI recommendations for the use of granulocyte and granulocyte macrophage colony-stimulating factors (G-CSF and GM-CSF) in preventing or treating chemotherapy-induced febrile neutropenia and infectious complications is provided in the following table. During development of their guideline, PGI considered the recommendations of other evidence-based guidelines, including those from ASCO.

Abbreviations used in the text and tables follow:

- ASCO, American Society of Clinical Oncology
- CSF, colony-stimulating factors
- G-CSF, granulocyte colony-stimulating factor
- GM-CSF, granulocyte macrophage colony-stimulating factor.
- PGI, Practice Guidelines Initiative

	ASCO (2000)	PGI (2003)
OBJECTIVE AND SCOPE	<ul style="list-style-type: none"> • To establish evidence-based clinical practice guidelines for the use of CSFs (referring to either G-CSF or GM-CSF) in patients who 	To evaluate if G-CSF and GM-CSF (jointly referred to as CSF) are effective in the management of adult cancer patients with

	<p>are not enrolled in clinical trials.</p> <ul style="list-style-type: none"> • To encourage reasonable use of hematopoietic CSFs to preserve effectiveness but discourage excess use when little marginal benefit is anticipated. 	<p>solid tumours (including lymphomas) who are receiving myelosuppressive chemotherapy.</p> <p>Specifically to evaluate:</p> <ul style="list-style-type: none"> • Whether CSF allows maintenance of chemotherapy dose, reduces important adverse clinical outcomes, and results in improved survival • Whether CSF allows dose intensification of chemotherapy and results in improved survival • Whether CSF during established episodes of febrile neutropenia improves outcomes such as survival, duration of fever, and days of hospitalization or on antibiotics and thus indirectly affects quality of life (QOL) • Whether the CSFs currently available for clinical use differ in their efficacies and toxicities • Whether the clinically available CSFs have differing doses and schedules that not only maintain efficacy but also have benefits in terms of convenience or cost • Whether CSF influences the occurrence or
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		resolution of chemotherapy-induced mucositis
INTENDED USERS	Oncologists	Oncologists
TARGET POPULATION	<ul style="list-style-type: none"> • United States • Adults and children with cancer undergoing cytotoxic treatment (i.e., myelosuppressive chemotherapy, myeloablative chemotherapy and bone marrow transplant). 	<ul style="list-style-type: none"> • Canada • Adult cancer patients with solid tumours receiving myelosuppressive chemotherapy <p>Note: With the exception of lymphoma, patients with hematologic malignancies are excluded.</p>
INTERVENTIONS AND PRACTICES CONSIDERED	<p>Prophylactic and therapeutic use of hematopoietic colony-stimulating factors (CSFs)</p> <p>CSFs commercially available in the United States:</p> <ul style="list-style-type: none"> • Granulocyte colony-stimulating factor (G-CSF; filgrastim; Escherichia coli-derived G-CSF; Neupogen [Amgen, Thousand Oaks, CA]) • Granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim; yeast-derived GM-CSF; Leukine [Immunex, Seattle, WA]) <p>CSFs under development in the United States:</p> <ul style="list-style-type: none"> • GM-CSF (molgramostim; E. 	<p>Prophylactic and therapeutic use of G-CSF and GM-CSF</p>

	<p>coli derived GM-CSF Leucomax [Schering-Plough, Madison, NJ and Sandoz, E. Hanover, NJ])</p> <p>CSFs developed primarily outside the United States:</p> <ul style="list-style-type: none"> • Lenograstim (G-CSF) • Regramostim (GM-CSF) • Ecogramostim (GM-CSF) 	
COMPARISON OF RECOMMENDATIONS FOR PROPHYLACTIC AND THERAPEUTIC USES		
To prevent neutropenia: Primary prophylaxis	<p>CSFs are recommended when the expected incidence of febrile neutropenia (based on the chemotherapy regimen) is greater than or equal to 40%. Thus, in general, for previously untreated patients receiving most chemotherapy regimens, primary administration of CSFs should not be used routinely.</p> <p>Primary CSF administration may be exceptionally warranted in patients at higher risk for chemotherapy-induced infectious complications even though the data supporting such use is not conclusive. Such risk factors might include the following: pre-existing neutropenia due to disease, extensive prior chemotherapy, or previous irradiation to the pelvis or other areas containing large amounts of bone marrow; a history</p>	<p>In the setting of standard-dose chemotherapy for solid tumours the risk of neutropenic fever is insufficient to justify routine use of CSF (which includes both granulocyte and granulocyte macrophage colony-stimulating factors) as primary prophylaxis.</p> <p>Qualifying statements:</p> <ul style="list-style-type: none"> • It is reasonable to suggest that primary prophylaxis with CSF is justified when the anticipated risk of febrile neutropenia is greater than 25-40%. However, such risks are rare with the majority of standard chemotherapy regimens for solid

	<p>of recurrent febrile neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity; or conditions potentially enhancing the risk of serious infection, e.g., poor performance status and more advanced cancer, decreased immune function, open wounds, or already-active tissue infections.</p>	<p>tumours, and evidence comes from cost analysis studies not specific to the Canadian health care system.</p> <ul style="list-style-type: none"> • CSF reduces the risk of febrile neutropenia associated with standard-dose chemotherapy; however, data are inconclusive as to whether quality of life is significantly improved by its use.
<p>To maintain chemotherapy dose-intensity in neutropenic patients or as secondary prophylaxis in patients with prior episodes of febrile neutropenia</p>	<ul style="list-style-type: none"> • In the setting of many tumors exclusive of curable tumors (e.g., germ cell tumors), dose reduction after an episode of severe neutropenia should be considered as the primary therapeutic option. No published regimens have demonstrated disease-free or overall survival benefits when the dose of chemotherapy was maintained and secondary prophylaxis was instituted. In the absence of clinical data or other compelling reasons to maintain chemotherapy dose-intensity, physicians should consider chemotherapy dose reduction after neutropenic fever or severe or prolonged neutropenia after the 	<p>If a patient experiences an episode of febrile neutropenia or prolonged neutropenia, dose reductions and/or delays of chemotherapy remain the standard initial approach. It is reasonable to use CSF to avoid multiple dose reductions or delays in circumstances where randomized controlled trials have shown improved survival with maintenance of dose intensity.</p> <p>Qualifying statements:</p> <ul style="list-style-type: none"> • Although reduced hospitalization and antibiotic use may be assumed to improve quality of life, dose maintenance with CSF may allow other significant toxicities to emerge

	previous cycle of treatment.	<p>(e.g., mucositis, anemia, thrombocytopenia, neuropathies), which can reduce quality of life. The inconvenience of daily injections of CSF and the cost are additional considerations if the risk of neutropenic fever is low.</p> <ul style="list-style-type: none"> • Since many patients still derive clinical benefit from commonly allowed chemotherapy dose reduction/delay, given the available data, it is not possible to define a cut-off point for acceptable dose reduction/delay before introducing CSF as secondary prophylaxis.
To allow dose intensification of chemotherapy	In the absence of more trials demonstrating a favorable effect on overall survival, disease-free survival, quality of life, or toxicity, there is no justification for the use of CSF to increase chemotherapy dose-intensity or schedule or both outside of a clinical trial. This application of CSF use remains the domain of appropriately designed clinical investigation.	The use of CSF to support the delivery of dose-intensified chemotherapy regimens can only be recommended in the context of randomized controlled trials evaluating regimens that seek to improve progression-free, disease-free, and/or overall survival.
To treat neutropenia	<ul style="list-style-type: none"> • Afebrile neutropenia: Intervention with a CSF in afebrile neutropenic patients 	Although data are limited, it is reasonable to use CSF to decrease duration of fever,

	<p>is not recommended.</p> <ul style="list-style-type: none"> • Febrile neutropenia: CSF should not routinely be used as adjunct therapy for the treatment of uncomplicated fever and neutropenia. Uncomplicated fever and neutropenia are defined as follows: fever of less than 10 days duration; no evidence of pneumonia, cellulitis, abscess, sinusitis, hypotension, multiorgan dysfunction, or invasive fungal infection, and no uncontrolled malignancies. Clinical trials have consistently shown a decrease in the duration of neutropenia of less than 500/microliter, but clinical benefit has not consistently accompanied the decreased duration of neutropenia. <p>Certain patients (i.e., profound neutropenia [absolute neutrophil count less than 100/microliter], uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction [sepsis syndrome], and invasive fungal infection) are at higher risk for infection-associated complications and have prognostic factors that are predictive of poor clinical outcome. The use of a CSF for such</p>	<p>antibiotic use, or hospitalization in patients with febrile neutropenia. Further studies are warranted to establish specific recommendations in this situation.</p> <p>Qualifying statements:</p> <ul style="list-style-type: none"> • Many patients with febrile neutropenia have a rapid and uncomplicated recovery on intravenous antibiotics. Although it may be reasonable to reserve CSF use for patients not achieving a rapid improvement (i.e., not defervescing within 48 hours on broad spectrum antibiotics or antibiotic therapy based on the sensitivity of the cultured organism), none of the reported trials assessed the use of CSF delayed in this way. Similarly, as recommended in the guidelines produced by ASCO, it may also be most reasonable to reserve CSF for patients with factors predictive of a poor outcome, e.g., profound neutropenia (absolute neutrophil count
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	<p>high-risk patients may be considered, but the benefits of a CSF in these circumstances have not been proven.</p>	<p><100/microliter), pneumonia, hypotension, multi-organ dysfunction, or invasive fungal infection.</p> <ul style="list-style-type: none"> • The efficacy of CSF may be limited in patients with febrile neutropenia or documented sepsis who have received dose-intensive chemotherapy, which is associated with a high risk of febrile neutropenia.
POTENTIAL HARMS ASSOCIATED WITH G-CSF		
Side effects of G-CSF	<p>The predominant side effect associated with administration of G-CSF has been medullary bone pain. In randomized trials, 15% to 39% of patients receiving approximately 5 micrograms/kg/d have described this symptom, compared with a 0% to 21% incidence in control patients. Less frequent side effects reported include exacerbations of preexisting inflammatory conditions, e.g., eczema, psoriasis, or vasculitis; rashes; allergic reactions; acute febrile neutrophilic dermatosis (Sweet syndrome); transient leukemia cutis, injection site reactions; mild alopecia; splenomegaly; splenic infarction; moderate reductions in platelet counts.</p>	<p>Toxicity of G-CSF is relatively mild. The most consistent clinical symptom attributed to G-CSF is bone pain reported in incidence rates ranging from 20% to 50% in three trials. With the exception of one case, reported bone pain was mild. Other commonly reported adverse effects include injection-site reactions, low-grade fever, headache, and skin rash. Indirect comparisons suggest that more adverse effects were associated with GM-CSF than with G-CSF.</p>

Guideline Content Comparison

The American Society of Clinical Oncology (ASCO) and the Practice Guidelines Initiative (PGI) present recommendations on the prophylactic and therapeutic use of colony-stimulating factors (G-CSF and GM-CSF) in cancer patients receiving myelosuppressive chemotherapy. Explicit rationale is provided for these recommendations.

The ASCO guideline is somewhat broader in scope than the PGI guideline. ASCO evaluates the evidence and presents recommendations, where possible, in the following areas that are not addressed by PGI in their focused guideline:

- Use of CSFs as adjuncts to progenitor-cell transplantation
- Use of CSFs in patients with acute leukemia and myelodysplastic syndromes (PGI restricts its guideline to adults with solid tumours, including lymphoma)
- Use of CSFs in patients receiving concurrent chemotherapy and irradiation
- Use of CSFs in the pediatric population
- Dosing and route of administration (although PGI examined currently available evidence on various doses or schedules of CSF, it concluded there are insufficient data to support specific recommendations)
- Initiation and duration of CSF administration

Both groups also evaluated evidence on the comparative clinical activity of G-CSF and GM-CSF but neither group provided firm recommendations for a specific type of CSF based on this evidence.

PGI also examined the use of CSF for preventing and treating chemotherapy-induced mucositis; however, the guideline developers felt there were insufficient data on which to make a recommendation. PGI plans to evaluate the use of G-CSF in patients undergoing bone marrow transplantation and the role of G-CSF/erythropoietin in patients with myelodysplasia in separate guidelines. PGI has also investigated the use of chemotherapy and growth factors in older patients with newly diagnosed, advanced-stage, aggressive histology non-Hodgkin's lymphoma in a separate guideline (see the National Guideline Clearinghouse summary [The Use of Chemotherapy and Growth Factors in Older Patients with Newly Diagnosed, Advanced-stage, Aggressive Histology Non-Hodgkin's Lymphoma](#)).

Areas of Agreement

ASCO and PGI agree that CSFs are not indicated as a routine prophylactic or therapeutic intervention in cancer patients receiving myelosuppressive chemotherapy. PGI considered the recommendations of other evidence-based guidelines, including those from ASCO, during development of their guideline. Both ASCO and PGI acknowledge that data supporting the use of CSF as primary prophylaxis in patients at high risk for febrile neutropenia and infectious complications are inconclusive. For this reason, both groups qualify their recommendations on use of prophylactic CSF in high-risk patients. PGI also agrees with the ASCO recommendation that dose reductions or delaying chemotherapy is the preferred approach in the majority of patients who have experienced prior episodes of febrile neutropenia. One exception to this recommendation is patients with potentially curable tumors, such as germ cell tumors, in whom maintenance

of dose intensity would allow for a cure or improved survival. PGI points out in its guideline, however, that there is no high-quality evidence supporting this restrictive use of CSF.

Neither group advocates use of CSFs to support dose intensification of chemotherapy outside the context of a randomized clinical trial.

There is also agreement that future clinical trials of CSFs should focus on survival, quality of life, and resource utilization.

Areas of Differences

ASCO and PGI differ somewhat in their recommendations concerning use of CSF for treatment of febrile neutropenia. ASCO recommends that CSF should be reserved for certain patients with profound neutropenia (absolute neutrophil count below 100/microliter) and other factors predictive of a poor outcome. PGI, while acknowledging the reasonableness of ASCO's approach, is less restrictive in its recommendation. PGI maintains that it is reasonable to use CSF to decrease the duration of fever, reduce antibiotic use, or decrease length of hospitalization in patients with febrile neutropenia. PGI notes, however, that further studies are needed to give a firm recommendation on appropriate use of CSF in febrile neutropenia.

This Synthesis was prepared by ECRI on October 8, 1999 and modified on December 11, 2000. It has been reviewed by the guideline developers as of January 5, 2001. This synthesis was updated most recently on June 29, 2004.

Internet citation: National Guideline Clearinghouse (NGC). Guideline synthesis: Use of colony stimulating factors in patients receiving chemotherapy. In: National Guideline Clearinghouse (NGC) [website]. Rockville (MD): 1999 Oct 8 (updated 2004 Jul 26). [cited YYYY Mon DD]. Available: <http://www.guideline.gov>.

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Date Modified: 11/1/2004

